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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/473,830	12/28/1999	JEFFREY M. LEIDEN	2844/53802	1518

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/473,830	LEIDEN ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-30,32,33,35-40,43 and 45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-30, 32, 33, 35-40, 43 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

3.0.0

DETAILED ACTION

Applicants' amendment filed 6-16-05 has been entered. Claim 2 has been amended. Claims 24-30, 32, 33, 35-40, 43 and 45 are pending and under consideration.

Double Patenting

1. Applicant is advised that should claim 24 be found allowable, claim 25 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Applicants' amendment filed 6-16-05 necessitates this new ground of rejection.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 24-30, 32, 33, 35-40, 43 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' amendment filed 6-16-05 necessitates this new ground of rejection.

Claim 24 has been amended to read "wherein at least 10% of the cardiomyocytes are transduced with the AAV and the AAV is present in the transduced cardiomyocytes for at least 4 weeks". The phrase "wherein at least 10% of the cardiomyocytes are transduced with the AAV and the AAV is present in the transduced cardiomyocytes for at least 4 weeks" is considered new matter. The amendment filed 6-16-05 fails to point out where in the specification has the support for the phrase set forth above. Page 11 of the specification discloses that hearts from C57BL/6 mice were explanted and perfused with $1.5x10^9$ IU of AAV CMV-LacZ for 15 minutes at 4^0C and by 4 weeks after perfusion, about 40% of the cardiomyocytes were beta-gal positive. The amended claims read on infusion of about $1x\ 10^5$ to about $1x10^9$ IU AAV/gram body weight into a coronary artery or coronary sinus of an animal and at least 10%, 40% or 50% of the cardipmyocytes are transduced with the AAV for at least 4 weeks. The specification only discloses perfusion with $1.5x10^9$ IU of AAV CMV-LacZ for 15 minutes at 4^0C and by 4 weeks after perfusion, about 40% of the cardiomyocytes were beta-gal positive. The specification fails to disclose infusion of about $1x\ 10^5$ to about $1x10^9$ IU AAV/**gram body weight** into a coronary artery or coronary sinus of an animal **and** at least 10%, 40% or 50% of the cardipmyocytes are transduced with the AAV **for** at least 4 weeks. It is unclear how many IU AAV/gram body weight corresponds to $1.5x10^9$ IU of AAV CMV-LacZ used. The specification fails to provide support for, specifically, at least 10% or at least 50% of cardiomyocytes transduced with the AAV **for** at least 4 weeks.

The claims also read on AAV being infused for at least about 2 minutes to about 30 minutes or for about 5 minutes to about 20 minutes and at least 10%, 40%, or 50% of the cardiomyocytes are transduced with the AAV for at least 4 weeks. The specification

only discloses that perfusion with $1.5x10^9$ IU of AAV CMV-LacZ for **15 minutes** at 4^0C and by 4 weeks after perfusion, about 40% of the cardiomyocytes were beta-gal positive. The specification fails to provide support for perfusion of at least about 2 minutes to about 30 minutes or for about 5 minutes to about 20 minutes and at least 10%, 40%, or 50% of the cardiomyocytes are transduced with the AAV for at least 4 weeks. In view of the reasons set forth above, the phrase "wherein at least 10% of the cardiomyocytes are transduced with the AAV and the AAV is present in the transduced cardiomyocytes for at least 4 weeks" is considered new matter.

4. Claims 24-30, 32, 33, 35-40, 43 and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for perfusing heart from C57BL/6 mice with $1.5x10^9$ IU of AAV CMV-LacZ for 15 minutes at 4^0C and by 4 weeks after perfusion, about 40% of the cardiomyocytes were beta-gal positive, does not reasonably provide enablement for stable and efficient transformation of cardiomyocytes by infusing about $1x\ 10^5$ to about $1x10^9$ IU AAV/gram body weight into a coronary artery or coronary sinus of an animal and at least 10%, 40% or 50% of the cardipmyocytes are transduced with the AAV for at least 4 weeks, wherein the AAV is infused for at least about 2 minutes to about 30 minutes, for about 5 minutes to about 20 minutes, or for about 15 minutes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants' amendment filed 6-16-05 necessitates this new ground of rejection.

The claims are directed to a method for stable and efficient transformation of cardiomyocytes by introducing an AAV vector expressing an angiogenic protein, such as FGF and VEGF, into cardiomyocytes via infusing said AAV vector into a coronary artery or a coronary sinus of an animal in an amount of $1x10^5$ to $1x10^9$ IU/gm, $1x10^7$ IU/gm, or $1x10^6$ to $1x10^8$ IU/gm body weight, wherein at least 10%, 40% or 50% of the cardipmyocytes are transduced with the AAV for at least 4 weeks. Claims 25-30, 32, 33 and 35-39 specify the percentage of cardiomyocytes being tranduced by the AAV virus and number of minutes the AAV virus IU is infused into coronary artery.

The claims encompass infusing about $1x\ 10^5$ to about $1x10^9$ IU AAV/gram body weight into a coronary artery or coronary sinus of an animal and at least 10%, 40% or 50% of the cardipmyocytes are transduced with the AAV for at least 4 weeks, wherein the AAV is infused for at least about 2 minutes to about 30 minutes, for about 5 minutes to about 20 minutes, or for about 15 minutes. The specification only discloses that hearts from C57BL/6 mice were explanted and perfused with **$1.5x10^9$ IU** of AAV CMV-LacZ for **15 minutes** at 4^0C and by 4 weeks after perfusion, about 40% of the cardiomyocytes were beta-gal positive.

The specification fails to provide adequate guidance and evidence for how to obtain at least 10%, 40% or 50% of the cardiomyocytes transduced with AAV vector for at least 4 weeks in an animal by infusing about $1x\ 10^5$ to about $1x10^9$ IU AAV/gram body weight into a coronary artery or coronary sinus of said animal and the AAV is infused for at least about 2 minutes to about 30 minutes, for about 5 minutes to about 20 minutes, or for about 15 minutes.

As mentioned by applicants in the amendment filed 6-16-05, Kaplitt et al., 1996 (Ann Thorac Surg, Vol. 62, p. 1669-1676) teaches infusing about $5x10^7$ units of AAVlac into coronary arteries of adult pigs and estimates that about 0.2% of the myocardial cells were beta-gal positive at 3 days after infusion (e.g. p. 1172, right column). It appears that the state of the art at the time of the invention held that the transduction efficiency of cardiomyocytes by AAV vector via intracoronary artery injection in an animal was pretty low (about 0.2% with $5x10^7$ AAV units injected). The specification fails to provide adequate guidance and evidence whether at least 10%, 40% or 50% of the cardiomyocytes would be transduced with AAV vector for at least 4 weeks in an animal by infusing about 1x 10^5 to about $1x10^9$ IU AAV/gram body weight into a coronary artery or coronary sinus of said animal and the AAV is infused for at least about 2 minutes to about 30 minutes, for about 5 minutes to about 20 minutes, or for about 15 minutes. The specification only discloses perfusion with $1.5x10^9$ IU of AAV CMV-LacZ for 15 minutes at 4^0C and by 4 weeks after perfusion about 40% of the cardiomyocytes were beta-gal positive. It is unclear how many IU AAV/gram body weight corresponds to $1.5x10^9$ IU of AAV CMV-LacZ used. The specification fails to demonstrate that infusion of about 1x 10^5 to about $1x10^9$ IU AAV/**gram body weight** into a coronary artery or coronary sinus of an animal would result in at least 10%, 40% or 50% of the cardipmyocytes being transduced with the AAV for at least 4 weeks. The specification also fails to demonstrate that perfusion of the recited dosage of AAV vector for at least about 2 minutes to about 30 minutes, for about 5 minutes to about 20 minutes, or for about 15 minutes would result in at least 10%, 40%, or 50% of the cardiomyocytes being transduced with the AAV for at least 4 weeks. In view of the reasons set forth above, one

skilled in the art at the time of the invention would not know how to infuse various dosage of the AAV vector via intracoronary artery or sinus injection for various injection durations in an animal to obtain at least 10%, 40%, or 50% of the cardiomyocytes being transduced with the AAV for at least 4 weeks.

For the reasons set forth above, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of one of ordinary skill which is high, the amount of experimentation required, and the breadth of the claims.

Conclusion

No claim is allowed.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER